DOPAMINE METABOLISM IN ISCHEMIC RAT CEREBRAL CORTEX

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ABSTRACT

Adult, male Sprague-Dawley rats subjected to 15 minutes of temporal unilateral common carotid artery occlusion and up to 6 hours of re-circulation was employed. The cortical concentration of dopamine (DA) and its metabolite (homovanillic acid, HVA) were determined by High Performance Liquid Chromatography with electrochemical detector. After 6 hours of recirculation, diminution of dopamine and accumulation of homovanillic acid (HVA) in ischemic cortex were detected. This finding strongly suggests that a postischemia increase release and turnover of dopamine, which may explain postischemic vasoconstriction.

Key Words : Delayed postischemic hypoperfusion, dopamine, homovanillic acid

INTRODUCTION

Patients with ischemic stroke often deteriorate while being observed hours or even days after the initial ictus. Delayed deterioration could be prevented if the responsible pathologic processed were understood. Release of vasoactive amines, formation of vasoactive products of arachidonic acid metabolism, and disturbance of calcium ion homeostasis in cerebrovascular smooth muscle may attribute to postischemic vasoconstriction[1].During the past decade, there has been a surge of interest in the possible relationship between brain monoamines and ischemic brain insults. Monoamine transmitters may play an important role in postischemic cerebral dysfunction. Monoamine may regulate cerebral reperfusion after ischemic insult and influence the recovery of brain ischemia.

The purpose of this investigation was to examine the change of dopamine (DA) and its metabolism homovanillic acid (HVA) in ischemic cerebral cortex, we have measured tissue level of DA and HVA in cerebral cortex of rat after transient ischemia. If DA do attribute to the morbidity of postischemic cerebral dysfunction, such change should be evidence at this time.

MATERIALS AND METHODS

Adult, male Sprague-Dawley rats weighting 250-300 gm were used. Animals were caged (three per cage) at constant temperature (about 27'C) in simulated day and night condition for 3 weeks prior to study and allowed free access to drinking water and chow.

The rats were anesthesized with ketamine hydrochloride (Ketalar, 100 mg / kg intraperitoneally). Left common carotid artery were exposed through ventral midline incision and artery, isolated from adjacent nerves and vesseles and clipped with Sugita aneurysm clip for 15 minutes, then was release. The animals were killed by dacapitation 1 hr and 6hrs after transient ischemia. The heads were severed, cooled in an ice bath, and the brains were removed (Lt : ischemia). Another group of rats subjected to sham operation without clipping the left common carotid artery. The concentration of DA and HVA were analyzed by High Performance Liquid Chromatograph with electrochemical detector. The mobile phase is a water-methanol mixture (7 : 93 for DA ; 3 : 97 for HVA), and the column is a E. Merk RP-18 endcapped column.

All values obtained from this experiment are expressed as mean±SEM. The significance between control and experimental data was determined by Student's t test.

RESULTS

The concentrations (mean±SEM) of DA and HVA in control and ischemic cortex were 384±64 and 746±54 ng per gram (n=8). The concentrations (mean±SEM) of DA and HVA in one hour after recirculation were 564±48 and 964±16 ng per gram (n=8). The concentration of DA and HVA in 6 hours after recirculation were 214±26 and 1684±124 ng per gram (n=8). Sham operation did not alter the levels of DA and HVA : the concentration of DA and HVA in these rats were 358±29 and 724±21 ng per gram.

DISCUSSION

In the recirculation period following cerebral ischemia, an initial " reactive " hyperemia is succeeded by a secondary decrease in cerebral blood flow (CBF), called delayed postischemic hypoperfusion[2-8]. Cerebral recovery may be hindered by poor perfusion rather than by immediate death of hypoxic nerve cells. The hyperemia may be explained by vasodilation due to tissue acidosis from lactic acid and carbon dioxide, or by a slight increase in extracellular potassium[9]. Some investigators have assigned a regulatory role in cerebral blood flow (CBF) to DA, and this concept has been supported by observed effects of DA on pial vessel diameter[10]. On the basis of the vasoactive properties of dopamine, it has been speculated that the increased turnover of this amine could lead to a deleterious vasoconstriction, which might cause additional cellular damage[11].

This study showed that deprivation of blood supply to the brain led to reduction of DA concentration in the cerebral cortex. This reduction is due to the increased release of this monoamine, since the rates of its synthesis and degradation are depressed after vascular occlusion. HVA concentration is increased in the brain following vascular occlusion, it is possible that HVA increased as the result of increased metabolism of DA release from its stores. Wurtman and Zervas[12] have postulated that an inappropriate loss of monoamine neurotranmitters may exacerate the pathophysiologic changes caused by initial ischemia. Reduction of DA concentration in cerebral cortex appeared at the time when adenosine triphosphate levels already were reduced for a long period. Unlike many other cell types, neuron in vivo appear incapable of using any other substance than glucose as their main energy source. Under normal circumstances, adenosine triphosphate, the energy source for the maintance of the electrochemical gradients, is efficiently

produced through aerobic glycolysis and oxidative phosphorylation. Cerebral ischemia which is characterized by deprivation of glucose and oxygen supply to the brain, inevitable led to ATP depletion. Therefore, it appears that release of DA in the brain is most probably related to a failure of the neuronal energy stores and the membrane transport following vascular occlusion[13]. Zervas and Wurtman et al.[14] have suggested that a fall in DA reflects release of transmitter DA into the extracellular fluid where it may have the effect of limiting capillary perfusion by vasoconstricting small vessels. The post-ischemic disruption of flow and metabolism, therefore, creates a potential for further brain damage. This secondary change might be prevented by appropriate therapeutic intervention because it occurs at time when patient are often under medical supervision.

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大鼠大腦皮質缺血時 Dopamine 代謝之研究

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雄性大鼠左側頸動脈以血管夾夾住十五分鐘後釋放，於再循環六小時後斷頭取出其大腦，以 High Performance Liquid Chromatography with electrochemical detector 測量左，右大腦皮質 Dopamine (DA)及其代謝物 homovanillic acid (HVA)的濃度。結果左側缺血大腦皮質 DA 含量減低而其代謝物 HVA 含量增加，對照組大腦皮質並無明顯變化。因此實驗結果，可認爲腦缺氧後 Dopamine 的釋取及轉變的增加是造成腦缺血後血管收縮的原因。